If you do not have amendments to the drawings, please delete this page.

REMARKS/ARGUMENTS

Claims 1-9, 11-19, 21 and 24-39 are pending in the application. Claims 24-38 were canceled without prejudice to subsequent revival and have been withdrawn from consideration. Claims 1-9, 11-19, 21 and 39 are under examination.

Claims 1, 11 and 14 have been amended. Entry of the amendment, reconsideration of the rejection, and allowance of claims 1-9, 11-19, 21 and 39 are requested. Claims 40-43 have been added. The new claims find support in claim 9, as filed.

Claim 39 was added in the amendment filed on March 22, 2004. Since the Examiner did not indicate whether or not claim 39 is allowable, the Applicants respectfully request clarification.

Applicants acknowledge the withdrawal of rejection of claim 6 under 35 U.S.C. §112, second paragraph.

The Amendment

In order to expedite prosecution of the application and advance the case toward allowance, the claims have been amended. No new matter was introduced by this amendment.

Claims 1, 11 and 14 have been amended to clarify that "the cell density of the biomass of the cell culture grown to confluence is increased *by reduction of working volume while the cells are bound to said microcarrier*". Support for this amendment can be found, for example, on page 6, paragraph [022], lines 5-6.

Rejection Under 35 U.S.C. §102(b)

Claims 1, 2, 4, 5, 11 and 12 remain rejected under 35 U.S.C. §102(b) as being allegedly anticipated by Caij *et al.* (*Arch. Virol.* (1989) 105:113-118). The Examiner indicates

that the claims do not recite that the cell density is increased in the microcarriers and further, the claims *do not specify the method by which density is increased.* According to the office action, the claimed method steps are the same as Caij's and hence, one would allegedly expect the same results. Specifically, it is asserted that Caij' cell density is increased when the microcarriers, cells, and virus are present (pages 113-115) and therefore the method steps allegedly read on the Applicants' method steps.

To the extent that the rejection applies to the claims as amended, the rejection is respectfully traversed.

The claims are drawn to a method of producing virus or viral antigen with cells bound to microcarriers, grown to confluence, infected with virus, incubated, harvested, and purified, wherein the cell density of the biomass of the cell culture is increased before or after infection. The claims have been amended to specify that the cell density of the biomass of the cell culture grown to confluence is increased *by reduction of working volume while the cells are bound to said microcarrier.* As such, the method by which the cell density is increased has been fully specified in the claims. This amendment was entered to advance prosecution and must not be construed as an acquiescence in the rejection.

It is also stated for clarification that the cells grow primarily on microcarriers (*i.e.*, on the surface of the microcarrier) as exemplified on page 12, paragraph [046], line 3. However, any type of microcarrier, including microcarriers with pores and/or channels (where cells may grow on, in or around the carrier), are within the scope of the invention (see page 6, paragraph [025]).

With respect to the amendment, the specification clearly describes how the cell culture grown to confluence is increased by reduction of working volume. As shown in the specification, for example, page 16, paragraph [054], lines 4-13, two 10 L bioreactor systems (Fermenters A and B) were loaded with the cell culture biomass. The two bioreactors have different total cell numbers, wherein Fermenter A has 1.2×10^{10} cells and Fermenter B has 2.4×10^{10} cells. Fermenter A contains 100% and fermenter B contains 200% cell biomass. Further, on page 12, paragraph [046], the specification teaches that **at the end of biomass production**

when cells have reached confluence growth, one part of the biomass reactor *volume* was reduced. This can be achieved by any method, for example, sedimentation, centrifugation, filtration, concentration via perfusion, and the like, as stated on page 6, paragraph [022] of the specification.

The ultimate virus yield per cell was increased compared to the virus yield of cells that are maintained at the same cell density as the original confluent cell culture, resulting in a total antigen concentration of 412.3 (495%) compared to 83.3 (100%) at confluent cell culture conditions (see TABLE 2, page 14). As previously indicated, this was *unexpected* because a higher cell density in a cell culture system normally leads to higher physiological stress (*e.g.*, cells slough off the microcarriers) and to a reduction of cell viability and less virus yield.

In comparison, Caij *et al.* teach a method of producing Togavirus in kidney cells in a culture medium supplemented with fetal calf serum, wherein the cells are first grown in Roux flasks (see page 113, last paragraph), subsequently transferred to microcarriers (see page 114, third paragraph), and further propagated via a conventional scale-up system by sub-passaging cells (see page 116, line 2). Although, Caij *et al.* indicate on page 113 (5th paragraph) that the goal of the study was to increase the virus titer by reducing the volume of growth medium, Caij *et al.* simply employed microcarriers. By using a microcarrier, the volume of *growth medium per cell* is naturally reduced since a greater number of cells are present in the medium. **However, Caij *et al.* do not increase the cell density of the biomass of the cell culture grown to confluence by reduction of working volume nor do they reduce their reactor volume.** In fact, Caij *et al.* compared a conventional monolayer system to a microcarrier culture and concluded that the microcarrier culture leads to increases virus yield (see page 116, second paragraph). Notably, Caij *et al.* do not describe or even suggest an actual reduction in reactor volume. As a result, Caij *et al.* do not anticipate the instant invention

In light of the amendment and arguments presented above, Applicants respectfully request that the rejection of claims 1, 2, 4, 5, 11 and 12 under 35 U.S.C. §102(b) be withdrawn.

Rejection Under 35 U.S.C. §103(a)

Claims 3, 6, 7-9, 13-19 and 21 remain rejected under 35 U.S.C. §103(a) as being allegedly obvious over Caij *et al.* and further in view of Kessler *et al.* (*Dev. Biol. Stand.* (1999) 98:13-21) and Merten *et al.* (*Dev. Biol. Stand.* (1999) 98:23-37), all of which are cited in the information disclosure statement of February 20, 2003.

To the extent that the rejection applies to the claims as amended, the rejection is respectfully traversed.

As discussed in the last response, Caij *et al.* do not even compare microcarrier cultures. Caij *et al.* only compare a microcarrier culture to a conventional monolayer system (see page 116, paragraph 2) and employ a conventional scale up process. As a result, the skilled artisan would have no motivation to consult Caij *et al.*

Since Caij *et al.* do not anticipate the instant invention (because Caij *et al.* do not disclose a method wherein the cell density of the biomass of the cell culture grown to confluence is increased by reduction of working volume), Caij *et al.*'s disclosure coupled with the knowledge that influenza virus can be produced in MDCK cells in the absence of serum (see Kessler *et al.*) and/or the knowledge that the production of influenza virus may be accomplished via serum-free microcarrier cultures using VERO and MDCK cells (see Merten *et al.*) does not teach the skilled artisan how to produce the claimed invention. There is simply no motivation to combine the references because applying Caij *et al.*'s method to Kessler *et al.* and/or Merten *et al.* would not lead to the claimed method.

In light of the amendment and arguments presented above, Applicants respectfully request that the rejection of claims 3, 6, 7-9, 13-19 and 21 under 35 U.S.C. §103(a), be withdrawn.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance and an action to that end is respectfully requested. If

a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at 415-576-0200.

Respectfully submitted,

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